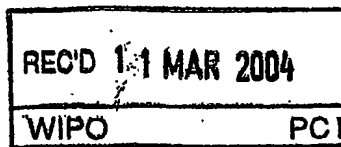




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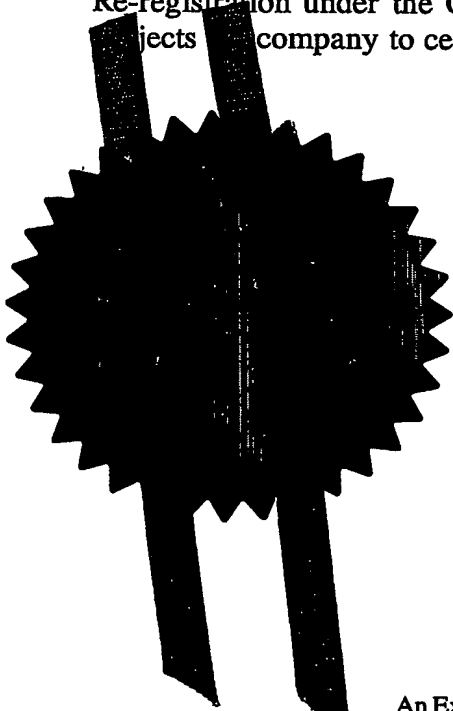
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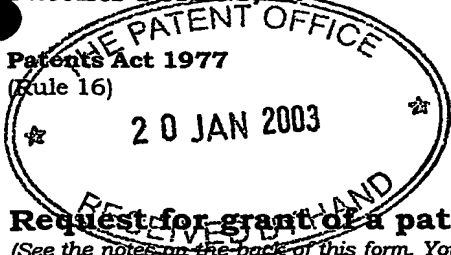
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1.	Your reference	4-32852P1	
2.	Patent application number (The Patent Office will fill in this part)	0301259.8	20 JAN 2003
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND	
	Patent ADP number (if you know it)		
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND	
4.	Title of invention	Organic compounds	
5.	Name of your agent (if you have one)	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH	
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	Patents ADP number (if you know it)	1800001	
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority ap num (if you k
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:	Yes	
	a) any applicant named in part 3 is not an inventor, or		
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Description 9

Claim(s) 1

Abstract

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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

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One

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I/We request the grant of a patent on the basis of this application

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Date

B. A. Yorke & Co.

B.A. Yorke & Co.

20 January 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. J. Crook

020 8560 5847

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Organic compounds

The present invention relates to a process for modifying the crystal habit of acicular drug substances, to the resulting crystallized drug substances and to pharmaceutical compositions comprising the same.

- 5 Industrial crystallization Inter alia aims at producing crystals of a defined quality such as shape, particle size and/or bulk density.

Usually, crystals grow in three directions, length, width and height. Some crystals however, have one or two preferred growth directions. For example, acicular substances e.g. crystals in the form of needles, rods or capillaries, have a preferred
10 crystal growth in one direction. The ratio between the length and the width of a crystal, the so-called aspect ratio, is significantly higher than 1:1 for acicular crystals; the higher the aspect ratio, the longer the crystal needles, rods or capillaries.

Acicular crystals often display poor processability, inefficient processing, e.g. for the manufacture of galenical formulations, tend to have a poor flowability and/or a low bulk
15 density, e.g. a bulk density of below about 200 kg/m³. Thus the formulation of e.g. tablets comprising said crystalline material may result in e.g. low mechanical stability of the formulation, an undesirably large dosage form and/or may require special compression methods.

It is thus desirable to modify the crystal habit, i.e. the relative rates of the growth of the
20 crystal in different directions, of acicular crystals. This may be achieved by retarding the crystal growth of the preferred growth direction, and/or enhancing the growth of the less preferred growth directions. Preferably, such a process does not have an effect on polymorphism.

Retardation of a crystal growth direction may be achieved e.g. by additives that act as
25 competitive agents and adsorb onto the fastest growing face and thus hinder crystal growth in this direction. In ice-cream technology this method is very well established. Carrageenan is added to inhibit needlelike growth of water crystals in order to avoid an "icy" taste. Another example is the addition of additives to diesel fuel in winter that prevents paraffin crystals from growing in long needles that would clog the fuel lines. In
30 case of a drug substance, the addition of an additive is however problematic.

Solvents have been used to influence the crystal habit of the solute, however, with an unsatisfactory effect.

Increase of particle size of acicular crystals has been achieved by temperature oscillation. When using temperature oscillation, crystals may however grow bigger
5 without changing or without changing substantially the crystal habit.

Temperature oscillation has been combined with sonication to modify the crystal habit of crystalline needles. The sonication limits the growth of the length of the needles by breaking them. Therefore, this process is not convenient for industrial crystallization as it may cause e.g. severe noise and abrasion of equipment.

10 Thus, there is a need for a crystallization process for acicular drug substances leading to improved crystal growth, particularly applicable to industrial manufacture.

Applicants have now found a process for modifying the crystal habit of acicular crystals of a drug substance yielding a crystalline drug substance with improved bulk density and/or a reduced mean aspect ratio. Additional steps, such as sonication or application
15 shear forces with high-shear mixers or homogenizers, for breaking the crystals, are not required.

The drug substance obtained in accordance with the process of the invention preferably has a bulk density above about 200 kg/m³, e.g. about 300 to about 600 kg/m³, and/or the mean aspect ratio is smaller than about 10:1, e.g. between about 1:1
20 and about 10:1, e.g. about 5:1, e.g. about 2:1.

Accordingly, the present invention provides a process for modifying the crystal habit of acicular drug substances comprising suspending said crystals in a solvent system having an effect on the crystal habit and subjecting said suspension to a temperature oscillation. In another embodiment, the present invention provides a process for
25 recrystallization of acicular drug substances comprising suspending said crystals in a solvent system having an effect on the crystal habit and subjecting said suspension to a temperature oscillation. The present invention further provides a process for producing crystals of an acicular drug substance having a bulk density of above about 200 kg/m³, preferably about 300 to about 600 kg/m³, and/or a mean aspect ratio of
30 below about 10:1, more preferably below about 5:1, even more preferably below about 2:1. The particle size of the crystals may be increased by said process.

The solvent system having an effect on the crystal habit retards the crystal growth of the preferred growth direction and/or enhances the crystal growth of the less preferred crystal faces. The effect of the solvent system on the crystal habit may be small and may be enhanced by temperature oscillation.

- 5 By "solvent system" is meant a solvent or solvent mixture comprising optionally an additive. The solvent system may be removed at the end of the crystallization process, e.g. evaporated when drying the processed crystals; preferably it is removed.

Typically, the solvent system is chosen in a way that chemical or physical interactions, e.g. hydrogen bonds or ionic bonds, between the solvent, solvents and/or additive and
10 the crystal face may be formed. Steric effects may also have to be considered to allow the solvent-crystal or additive-crystal interaction. E.g. in the case of an ionic compound, preferably a polar solvent or additive is chosen, and in case of hydrogen-binding compounds, preferably a hydrogen bond-donor or acceptor solvent or additive is chosen.

15 Suitable solvents are those known to the skilled person, such as

- a) a polar protic solvent such as an alkanol e.g. a C₁₋₆ alkanol, preferably a C₁₋₄ alkanol, wherein the alkyl radical may be linear or branched such as methanol, ethanol or isopropanol; or a cycloalkanol, e.g. cyclohexanol; water; an organic acid e.g. a C₁₋₆ carboxylic acid, e.g. acetic acid,
- 20 b) a dipolar aprotic solvent such as an ester e.g. a carboxylic acid ester e.g. isopropyl acetate, ethyl acetate; a ketone e.g. acetone; an ether e.g. diethyl ether, methyl *t*-butyl ether; an amide e.g. formamide, dimethylformamide; dimethylsulfoxide; a nitrile e.g. acetonitrile,
- c) a non-polar solvent such as an alkane e.g. hexane or heptane, a cycloalkane, e.g.
25 cyclohexane; or an aromatic hydrocarbon, e.g. toluene or xylene; or
- d) any mixture thereof.

Suitable additives are those known to the skilled person e.g. those described in J. Nyvlt and J. Ulrich "Admixtures in Crystallization" (VCH Weinheim, 1995), the contents thereof being incorporated herein by reference. The additive may be present in an
30 amount of about 1 ppm to about 10% by weight of the drug substance.

The crystalline suspension is prepared by methods known to a skilled person. Typically, the crystals are dispersed in a solvent system so that a significant amount of

drug substance, e.g. less than 70% by weight, e.g. less than 50% by weight, e.g. about 10 to about 30% by weight of drug substance, dissolves upon heating and recrystallizes upon cooling.

5 The temperature oscillation is performed by heating and cooling the crystalline suspension to predetermined temperature, conveniently under stirring. The parameters for the temperature oscillation depend upon the nature of the solvent or solvent mixture, the nature of the crystals, the desired particle size and/or desired bulk density and may be optimized using standard tests. The particle size of the processed crystals may be assessed e.g. by microscopy.

10 The mean temperature and the temperature amplitude may be chosen to bring a significant amount of drug substance into solution, e.g. between 10 and 30% of drug substance. Typically, the temperature amplitude may be about e.g. about $\pm 1^{\circ}\text{C}$ to about $\pm 20^{\circ}\text{C}$, e.g. about $\pm 5^{\circ}\text{C}$ to $\pm 10^{\circ}\text{C}$. The temperature amplitude may be different or the same for each oscillation, preferably it is the same for each oscillation.

15 The temperature oscillation curve may be in the form of approximately a sinus curve with a temperature holding step or approximately a zig-zag curve, i.e. a curve comprising a substantially linear heating step and a substantially linear cooling step. Preferably, the temperature oscillation curve is approximately a zig-zag curve, more preferably with the same temperature amplitude. Typically, the oscillation starts with
20 heating of the suspension.

In order to avoid total process time of several days, e.g. of more than two days, heating time and cooling time may be each e.g. about 20 to about 120 minutes, e.g. about 80 minutes. Between heating and cooling, there may be a temperature holding step, e.g. of a duration of about 5 min. Preferably, the heating time may be shorter
25 than the cooling time, e.g. the heating time may be about 25 minutes and the cooling time may be about 80 minutes.

In general, the higher the number of oscillations, the more the aspect ratio tends towards 1:1 and the larger the particles. Practically, the number of oscillations may be about 6 to about 16, e.g. about 8 to about 10, oscillations.

30 Finally, the suspension is cooled to a temperature below about 23°C in order to reduce the solubility of the crystals in the solvent system. Addition of a further solvent wherein

the crystals have a low solubility may increase the yield of the process. Finally, the crystals are filtered and dried. Drying of the crystals, e.g. in a rotary dryer, may further increase the bulk density.

5 In particular, the present invention relates to acicular drug substances such as mycophenolic acid, mycophenolate salt or derivatives thereof in acicular form, preferably mycophenolate salt.

10 The mycophenolic acid or mycophenolate salt preferably is in an amount of about 95%, preferably about 98%, even more preferably about 100%, in the form of its anhydrate. Examples of mycophenolate salts include e.g. cationic salts of mycophenolic acid, e.g. of alkali metals, especially the sodium salt. Preferred salt is the mono-sodium salt.

The crystals obtained by the process of the invention have an aspect ratio of about 10:1 to about 1:1, e.g. about 5:1 to about 2:1, and/or a bulk density of above about 200 kg/m³, e.g. of between about 300 and about 600 kg/m³, e.g. 500 kg/m³.

15 In accordance with the foregoing the present invention further provides crystals of mycophenolic acid, mycophenolate salt or derivatives thereof in acicular form with an aspect ratio of about 10:1 to 1:1 and/or a bulk density of above about 200 kg/m³, e.g. prepared by the process of the invention described herein. A preferred solvent system is a mixture of polar protic solvents, e.g. a mixture of water and an alkanol such as
20 indicated above. A typical temperature oscillation is at a mean temperature of 42-47°C with an amplitude of $\pm 5-7^{\circ}\text{C}$

The crystals of the invention may be formulated for administration in any convenient way, e.g. in the form of tablets. Tablets may be obtained e.g. by granulation of the crystals of the invention followed by compression. Tablets comprising crystals of the
25 invention have an improved hardness, e.g. a hardness of about 130N to about 160N. The abrasion is less than about 0.5%, e.g. less than about 0.3%. Tablets may be coated tablets, e.g. enteric coated tablets. Suitable coating material comprises, e.g. hydroxypropyl methylcellulose phthalates, e.g. HPMCP HP50, and optionally pigments, e.g. iron oxide, indigotine, e.g. indigotine lake, and/or titanium dioxide.

30 Tableting procedures which may be used may be conventional or known in the art or based on such procedures e.g. those described in L. Lachman et al. The Theory and

Practice of Industrial Pharmacy, 3rd Ed, 1986, H. Sucker et al, Pharmazeutische Technologie, Thieme, 1991, Hagers Handbuch der pharmazeutischen Praxis, 4th Ed. (Springer Verlag, 1971) and Remington's Pharmaceutical Sciences, 13th Ed., (Mack Publ., Co., 1970) or later editions.

- 5 Accordingly, in another aspect, the present invention provides a pharmaceutical composition, e.g. in the form of tablets, comprising crystals of the invention, and a pharmaceutically acceptable carrier.

10 In another aspect, the present invention provides drug substance crystals of the invention for use as a pharmaceutical or in the preparation of a pharmaceutical composition for use in any method described in the art for said drug substance. Furthermore, the present invention provides the use of crystals and the pharmaceutical compositions of the invention for the preparation of a medicament for the treatment of any condition known therefore and described in the art.

15 The compositions of the invention comprising mycophenolic acid or a mycophenolate salt are useful as immunosuppressants as indicated by standard tests. The activity and characteristics of the compositions of the invention may be indicated in standard clinical trials or animal test as described e.g. in WO 97/38689, the content of which is incorporated herein by reference.

20 The pharmaceutical compositions of the invention comprising mycophenolic acid, mycophenolate salt or acicular derivatives thereof are useful as immunosuppressants and in particular for the following conditions:

- 25 a) Treatment and prevention of native or transgenic organ, tissue or cellular allograft or xenograft transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, pancreatic islet cell, neural cell or corneal transplant; including treatment and prevention of acute rejection; treatment and prevention of hyperacute rejection, e.g. as associated with xenograft rejection; and treatment and prevention of chronic rejection, e.g. as associated with graft-vessel disease. The compositions of the invention are also indicated for the treatment and prevention of graft-versus-host disease, such as
- 30 following bone marrow transplantation.
- b) Treatment and prevention of autoimmune disease, e.g. immune-mediated disease and inflammatory conditions, in particular inflammatory conditions with an etiology including an immunological component such as arthritis (for example rheumatoid

arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific immune-mediated disease for which the compositions of the invention may be employed include, autoimmune hematological disorders, including, but not limited to hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulosis, dermatomyositis, polymyositis, chronic active hepatitis, primary biliary cirrhosis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, pemphigus, idiopathic sprue, inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves disease sarcoidosis, multiple sclerosis, juvenile diabetes (diabetes mellitus type I), non-infectious uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, vasculitis, glomerulonephritides (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy) and juvenile dermatomyositis.

For the above uses the required dosage will of course vary depending on the drug substance used, the mode of administration, the particular condition to be treated and the effect desired.

Accordingly, the present invention further provides a method for treating and/or preventing native or transgenic organ, tissue or cellular acute or chronic allograft or xenograft transplant rejection or graft-versus-host diseases, or treating and/or preventing an autoimmune disease, e.g. as disclosed above, in a subject, such as a human or other animal subject, comprising administering to the subject an effective amount of comprising crystals of the invention of mycophenolic acid, mycophenolate salt or derivatives thereof.

The following Examples serve to illustrate the invention.

Example 1:

Fine long rods of mycophenolate mono-sodium salt are obtained by crystallization from isopropanol, filtration and drying at 50°C in a paddle dryer. The crystals have a mean length of 20-50 μm , a mean width of about 1 μm and a bulk density of about 180-200 kg/m^3 . The crystal habit of these crystals is modified as described in Examples 2 to 6.

Examples 2 to 5:

40 g of mycophenolate mono-sodium salt crystallized as described in Example 1 are suspended in 120 g of methanol/water in a mixing ratio of 95/5 in a stirred vessel. The suspension is oscillated at a mean temperature of 44°C with an amplitude of +/- 6°C.

- 5 The period of one oscillation is 110 min, the number of oscillations is given in Table 1. The process temperature is controlled in a way that it performs a zigzag-curve over time.

240 g of ethanol are added and the suspension is cooled to 0°C within 3h. After filtration and drying in a rotary dryer, large compact crystals are obtained. The final bulk density is given in Table 1.

10

Table 1:

	Ex. 2	Ex. 3	Ex. 4	Ex. 5
number of oscillations	5	6	10	16
bulk density [kg/m ³]	280	310	380	490

Similarly, the mycophenolate mono-sodium salt may be suspended in methanol/water in another mixing ratio ranging between about 98:2 and 90:10.

Example 6:

- 15 20 g of mycophenolate mono-sodium salt crystallized as described in Example 1 are suspended in 60 g of methanol/water in a mixing ratio of 95/5 in a stirred vessel. The suspension is oscillated at a mean temperature of 44°C with an amplitude of +/- 6°C. The period of one oscillation is 160 min, the number of oscillations is 8. The process temperature is controlled in a way that it performs a sinus-curve over time.

- 20 180 g of ethanol are added during 180 min whereby the oscillation is continued. Then the suspension is cooled to 0°C within 3h. After 2h, the crystals are filtered and dried in a rotary dryer. The final bulk density is 350 kg/m³.

Example 7:

Component	amount in [mg]	amount in [mg]
Mycophenolate sodium	192.4	384.8
Anhydrous lactose	45.0	90.0
Crospovidone	32.5	65.0

Component	amount in [mg]	amount in [mg]
Povidone K30 PH	20.0	40.0
Maize Starch	10.3	20.5
Colloidal silicon dioxide	6.6	13.2
Magnesium stearate	3.3	6.5
Enteric coating:		
Hypromellose phthalate HP50	42.0	65.0
Titanium dioxide	2.9	4.7
Iron oxide yellow	0.08	0.17
Iron oxide red	-	0.17
Indigo carmine	0.039	-

Mycophenolate sodium; Povidone® K30, silica, colloidal anhydrous are mixed, wet-granulated using ethanol 94% (w/w), mixed with lactose anhydrous, maize starch, Crospovidone®, and magnesium stearate; and compressed to tablets.

- 5 The tablets are coated in a perforated pan coater with a solution of the coating ingredients in ethanol (with 5% isopropanol) / acetone.

The tablets have a hardness of 130 to 156 KN. Abrasion is less than 0.3%.

CLAIMS

1. Process for modifying the crystal habit of an acicular drug substance comprising suspending said crystalline drug substance in a solvent system having an effect on the crystal habit and subjecting said suspension to a temperature oscillation.
- 5 2. Process for recrystallising an acicular drug substance comprising suspending said crystals in a solvent system having an effect on the crystal habit and subjecting said suspension to a temperature oscillation.
3. Process according to claim 1 or 2 wherein the crystal habit is modified in that the mean aspect ratio of the processed crystals is smaller than about 10:1.
- 10 4. Process according to any one of claims 1 to 3 wherein the drug substance after temperature oscillation has a bulk density of about above 200 kg/m³.
5. Process according to any preceding claim wherein the temperature oscillation is in form of a zig-zag curve.
- 15 6. A process according to any one of claims 1 to 5 for producing crystals having a mean aspect ratio of the processed crystals smaller than about 10:1 or a bulk density of about 200 kg/m³.
7. Crystals of an acicular drug substance with an aspect ratio of about 10:1 to 1:1 and/or a bulk density of above about 200 kg/m³.
8. Crystals according to claim 7 wherein the acicular drug substance is
20 mycophenolic acid, mycophenolate salt or a derivative thereof.
9. A pharmaceutical composition, e.g. in the form of tablets, comprising crystals of claim 7 or 8 in association with a pharmaceutically acceptable carrier.
10. Crystals of claim 8 for use as a pharmaceutical.
11. A process substantially as described in the examples.
- 25 12. Crystals substantially as described in the examples.

* * *

PCT Application
PCT/EP2004/000354

